

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Nobuyuki Itoh et al.
Application No. : 10/060,765
5 Filed : January 29, 2002
For : HUMAN FGF-21 GENE AND GENE EXPRESSION
PRODUCTS

Examiner : Ruixiang Li
Art Unit : 1646
10 Docket No. : 60219-13
Date : April 5, 2005

Mail Stop Amendment
Commissioner for Patents
15 P.O. Box 1450
Alexandria, VA 22313-1450

AFFIDAVIT OF DR. MICHAEL KAVANAUGH UNDER 37 C.F.R. § 1.131

20 Sir:

I, Michael Kavanaugh, M.D., being duly sworn, say:

1. I am an internationally recognized scientist and am presently employed as
Senior Director, Research, at Chiron Corporation, Emeryville, California (employed at
25 Chiron Corporation from 1994 to present). I received a Bachelors Degree in Molecular
Biophysics and Biochemistry from Yale University in 1978 and a M.D. degree from
Vanderbilt Medical School in 1983.

2. I am an author or co-author of more than 20 peer-reviewed research
articles and have been invited to give numerous presentations on my research at
30 national and international meetings. Prior to joining Chiron Corporation I practiced
medicine at the University of California, where I maintain appointments as Associate
Clinical Professor of Medicine, and Attending Physician, VAMC, Intensive Care Unit,
San Francisco. My curriculum vitae is attached as Exhibit 1.

2. I am an author or co-author of more than 20 peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Chiron Corporation I practiced medicine at the University of California, where I maintain appointments as Associate
5 Clinical Professor of Medicine, and Attending Physician, VAMC, Intensive Care Unit, San Francisco. My curriculum vitae is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 102(e), over Agarwal, U.S. Patent Publication 2001/001262801, filing date November 5, 1999.

10 4. On information and belief, the earliest filing date to which the Agarwal publication is entitled is November 5, 1999.

5. Prior to November 5, 1999, applicants were in possession of the amino acid sequence of FGF-21, identified in the present application, and in our priority application (Serial No. 60/166,540, filed November 18, 1999), as SEQ ID NO:4.

15 Attached as Exhibit 2 is a copy of the amino acid sequence of SEQ ID NO:4. Epitopes of this polypeptide were also invented prior to November 5, 1999, as evidenced by our identification of exemplary epitope peptides, later assigned SEQ ID NO:7 and SEQ ID NO:8 (Exhibit 3). These peptides are disclosed at page 30, lines 12-21 of the first
20 provisional application, Serial No. 60/166,540, filed on November 18, 1999. In summary, applicants were in possession of the claimed subject matter in the United States, prior to November 5, 1999.

6. I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under
25 § 1001 of Title 18 of the United States Code.

William Michael Kavanaugh

William Michael Kavanaugh

5 State of California)
County of Alameda) ss.

10 On this 5th day of April, 2005, before me, a Notary Public in and
for the State and County aforesaid, personally appeared William Michael Kavanaugh, to
me known and known to me to be the person of that name, who signed and sealed the
foregoing instrument, and he acknowledged the same to be his free act and deed.

15 *Elissa M. Nash*
Notary Public

Commission expires February 19, 2009

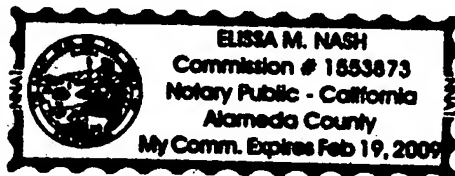


Exhibit 1

William Michael Kavanaugh, M.D.

Curriculum vitae

PERSONAL DATA

Maritus Status: Married, 1 child Citizenship: USA Residence: Orinda, CA

Work Address: Chiron Corporation
4560 Horton Street, Rm 4.4144
Emeryville, CA 94608
(510) 923-4042 Fax: (510) 923-5550
email: Mike_Kavanaugh@chiron.com

EDUCATION

Undergraduate: Yale University, B.A., Molecular Biophysics and Biochemistry, 1978
Medical School: Vanderbilt Medical School, M.D., 1983

EMPLOYMENT AND EXPERIENCE

Academic/Clinical

| | |
|----------------|--|
| 7/83 - 6/84 | Internship, Internal Medicine, University of California, San Francisco |
| 7/84 - 6/86 | Residency, Internal Medicine, University of California, San Francisco |
| 7/86 - 6/88 | Research Fellow, Cardiovascular Research Institute, L.T. Williams laboratory, University of California, San Francisco |
| 7/88 - 12/89 | Clinical Fellow in Cardiology, University of California, San Francisco |
| 3/90 - 6/92 | Instructor in Medicine, University of California, San Francisco |
| 7/92 - 6/95 | Assistant Adjunct Professor of Medicine, UCSF |
| 8/96 - 7/01 | Assistant Clinical Professor of Medicine, UCSF |
| 7/01-present | Associate Clinical Professor of Medicine, UCSF |
| 1/90 - present | Attending Physician, VAMC, Intensive Care Unit, San Francisco (WOC) |

Industry

| | |
|----------------|---|
| 11/94 - 4/95 | Principal Scientist, Chiron Corporation |
| 4/95 - 9/95 | Senior Scientist, Chiron Corporation |
| 9/95 - 3/97 | Associate Director of Biology Discovery, Chiron Corporation |
| 3/97 - 1/99 | Director, Biological Discovery, Chiron Corporation |
| 1/99 - present | Senior Director, Research, Chiron Corporation |

HONORS, AWARDS AND LICENSES

| | |
|-----------|---|
| 5/78 | B.A. <i>magna cum laude</i> , Molecular Biophysics and Biochemistry, Yale University |
| 8/81 | Alpha Omega Alpha medical honor society |
| 5/83 | Graduated first in class, Vanderbilt Medical School -Upjohn Award for Excellence, Vanderbilt Medical School -Founder's Medal, Vanderbilt Medical School |
| 1984 | California Medical License (active, #G53774) |
| 7/86 | American Heart Association Fellowship Grant |
| 11/86 | National Research Service Award (NIH - 2 years) |
| 9/86 | Board Certified, Internal Medicine (active, #109439) |
| 9/88 | American Federation for Clinical Research |
| 11/89 | Board Certified, Cardiology (active, #109439) |
| 3/90 | Physician Scientist Award (NIH - 5 years) |
| 9/91 | Fellow, Program of Excellence in Molecular Biology |
| 1997-2000 | AHA Western States Affiliate Grant Peer Review Committee |

RESEARCH INTERESTS AND EXPERIENCE

- ♦ Growth Factors, Cytokines, Chemokines, Receptors, Intracellular Signaling, Therapeutic Proteins, Antibodies, Protein Engineering
- ♦ Molecular Biology, Cell Biology, Protein Biochemistry, Preclinical Pharmacology
- ♦ Cancer Biology And Immunology, Cardiovascular Biology and Physiology, Wound Healing
- ♦ Gene Discovery, Target Discovery And Validation, Therapeutic Protein Discovery And Development Including Therapeutic Antibodies, Small Molecule Discovery, Gene Therapy Research
- ♦ Preclinical And Clinical Development Through Phase III Planning, Practicing Physician
- ♦ Research Management, Project Management, Program Management
- ♦ Current Positions: Leader, Therapeutic Antibody Research Program, Chiron; Attending Physician, ICU, San Francisco VA Medical Center; Associate Clinical Professor of Medicine, UCSF

ISSUED PATENTS AND PUBLISHED PATENT APPLICATIONS

US patent #5744313. Assay employing novel protein domain which binds tyrosine phosphorylated proteins. 4/28/98

US patent #5925547. Nucleic acid encoding novel protein domain which binds tyrosine phosphorylated proteins 7/20/1999

US patent #6090621. Signaling inositol polyphosphate 5-phosphatases (SIPs) 07/18/2000

US patent #6280964. Binding sites for phosphotyrosine binding domains 08/28/2001

WO 97/40173 PI 3-kinase fusion mutants and uses thereof

WO 98/00539 Mitogen-activated protein kinase) kinase-3 (mkk3) interacting protein (MIP)

WO 00/18921 Synthetic peptides having FGF receptor affinity

WO 00/21548 Angiogenically effective unit dose of FGF and method of administering

WO 00/46380 Fibroblast growth factor receptor-immunoglobulin fusion protein
WO 00/56890 Human FGF gene and gene expression products
WO 01/13031 Dose of an angiogenic factor and method of administering to improve myocardial blood flow
WO 01/14415 EGFH2 genes and gene products
WO 01/31008 Human FGF-20 gene and gene expression products
WO 01/36640 Human FGF-21 gene and gene expression products
WO 01/66595 Human FGF-23 gene and gene expression products

REPRESENTATIVE PUBLICATIONS

Spicer EK, **Kavanaugh WM**, Dallas WS, Falkow S, Konigsberg WH, and Schafer DE (1981) Sequence Homologies Between A Subunits of *Escherichia coli* and *Vibrio cholera* Enterotoxins. *Proc. Natl. Acad. Sci. U.S.A.* **78**: 50-54.

Kavanaugh WM, Williams LT, Ives HE, and Coughlin SR (1988) Serotonin-Induced Deoxynucleic Acid Synthesis in Vascular Smooth Muscle Cells Involves a Novel, Pertussis Toxin-Sensitive Pathway. *Molecular Endocrinology* **123**: 599-605.

Kavanaugh WM, Harsh IV GR, Starksen NF, Rocco CM, and Williams LT (1988) Transcriptional Regulation of the A and B Chain Genes of Platelet-Derived Growth Factor in Microvascular Endothelial Cells. *J. Biol. Chem.* **263**: 8470-8472.

Harsh IV GR, **Kavanaugh WM**, Starksen NF and Williams LT (1989) Cyclic AMP Blocks Expression of the c-sis Gene in Tumor Cells. *Oncogene Research* **4**: 65-73.

Escobedo, JA, Kaplan, DR, **Kavanaugh WM**, Turck, CW and Williams, LT (1991) A Phosphatidylinositol-3 Kinase Binds to Platelet-Derived Growth Factor Receptors Through a Specific Receptor Sequence Containing Phosphotyrosine. *Mole. Cell. Biol.* **11**:1125-1132.

Escobedo, JA, Navankasattusas, S, **Kavanaugh WM**, Milfay, D, Fried, VA and Williams, LT (1991) cDNA Cloning of a Novel 85 Kd Protein That Has SH2 Domains and Regulates Binding of PI3- Kinase to the PDGF β -Receptor. *Cell* **65**:75-82.

Turck, CW, Escobedo, JA, **Kavanaugh WM**, and Williams, LT. (1991) Structural and Functional Characterization of a Synthetic Phosphorylated Peptide Derived from the PDGF β -Receptor. *Pept. Res.* **4**: 36-39.

Kavanaugh WM, Klippel, A, Escobedo, JA and Williams, LT. (1992) Modification of the 85 kD Subunit of Phosphatidylinositol 3' Kinase in Platelet-Derived Growth Factor-Stimulated Cells *Mole. Cell. Biol.* **12**: 3415-3424.

Kavanaugh WM. Platelet-Derived Growth Factor: Future Directions in the Prevention of Restenosis. (1993) In: Interventional Cardiology: Future Directions, 2nd Edition, John HK Vogel, and Spencer B. King, Eds. Mosby-Yearbook, Littleton, MA

- Kavanaugh, WM, Turck, Klippel, A and Williams, LT. (1994)** Tyrosine 508 of the 85 kDa Subunit of Phosphatidylinositol 3-Kinase is Phosphorylated by the Platelet-Derived Growth Factor Receptor. *Biochemistry* **33** (36): 11046-11050.
- Kavanaugh, WM and Williams, LT. (1994)** An Alternative to SH2 domains for Binding Tyrosine-Phosphorylated Proteins. *Science* **266**:1862-1865.
- Kavanaugh, WM, Turck, CW and Williams, LT. (1995)** PTB Domain Binding to Signaling Proteins through a Sequence Motif Containing Phosphotyrosine. *Science* **268**:1177-1179.
- Lamiet, A.A., Apell, J., Conroy, L., and Kavanaugh, W.M. (1995)** Affinity, Specificity and Kinetics of the Interaction of the SHC PTB Domain with N-X-X-phosphotyrosine Motifs of Growth Factor Receptors. *J. Biol. Chem* **271** (1):264-269.
- Kavanaugh, WM, Pot, DA, Chin, S.M., Deuter-Rienhard, M, Jefferson, AB, Norris, FA, Masiarz, FR, Cousens, LS, Majerus, PW and Williams, LT. (1996)** Multiple Forms of an Inositol Polyphosphate 5-Phosphatase form Signaling Complexes with SHC and GRB2. *Curr. Biol.* **6**(4):438-445.
- Kavanaugh, WM and Williams, LT. (1996)** Signaling Through Tyrosine Kinase Receptors. In: Modular Texts in Molecular and Cell Biology, Vol. 1: Signal Transduction (C-H. Heldin and M. Purton, eds.), pp.3-18, Chapman & Hall, London.
- Klippel, A, Reinhard, CA, Kavanaugh, WM, Apell, G, Escobedo, M-A., and Williams, LT. (1996)** Membrane Localization of Phosphatidylinositol 3' Kinase is Sufficient to Activate Multiple Signal-Transducing Kinase Pathways. *Mole. Cell. Biol.*, **16**(8):4117-4127.
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- Deuter-Reinhard, M, Apell, G., Pot, DA, Klippel, A, Williams, LT, and Kavanaugh, WM. (1997)** SIP/SHIP inhibits *Xenopus* Oocyte Maturation Induced by Insulin and Phosphatidylinositol 3-Kinase. *Mole. Cell. Biol.*, **17**(5):2559-2565.
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- Klippel, A, Escobedo, M-A, Wachowicz, MS, Apell, G, Brown, TW, Giedlin, MA, Kavanaugh, WM, and Williams, LT. (1998)** Activation of Phosphatidylinositol 3-kinase is Sufficient for Cell Cycle Entry and Promotes Cellular Changes Characteristic of Oncogenic Transformation. *Mole. Cell. Biol.*, **18**(10): 5699-5711.
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Wisniewski, D, Strife, A, Seldman, S, Erdjument-Bromage, H, Gnanas, S, **Kavanaugh, WM**, Tempst, P, and Clarkson, B. (1999) A Novel SH2-Containing Phosphatidylinositol 3,4,5-Trisphosphate 5-Phosphatase (SHIP2) is Constitutively Tyrosine Phosphorylated and Associated with SHC in Chronic Myelogenous Leukemia Progenitor Cells. *Blood*, **93**(8):1-15.

Vollenweider, P, Clodi, M, Martin, SS, Imamura, T, **Kavanaugh, WM**, and Olefsky, JM. (1999) A SH2 domain-containing 5' Inositolphosphatase Inhibits Insulin-induced GLUT4 Translocation and Growth Factor-induced Actin Filament Rearrangement. *Mole. Cell. Biol.*, **19**(2):1081-91.

Ballinger, M.D., Shyamala, V., Forrest, L.D., Deuter-Reinhard, M., Doyle, L.V., Wang, J-X., Panganiban-Lustan, L., Stratton, J.R., Apell, G., Winter, J., Doyle, M.V., Rosenberg, S., and **Kavanaugh, W.M.** (1999) Semi-rational Design of a Potent, Artificial Agonist of Fibroblast Growth Factor Receptors. *Nature Biotech.* **17**:1199-1204.

Liu, C, Deuter-Reinhard, M, Terjung, R and **Kavanaugh, WM**. (manuscript in preparation) Hypoxia Enhances the Proliferative Response of Endothelial and Fibroblast Cell Lines to Multiple Mitogens.

Abraham, JA, Yeng, S, Terjung, R and **Kavanaugh, WM**. (manuscript in preparation). Therapeutic Benefit of Intramuscular Delivery of FGF-2 in a Rat Model of Peripheral Vascular Disease.

Abraham, JA, Yeng, S, Terjung, R and **Kavanaugh, WM** (manuscript in preparation). Prolongation of the Therapeutic Effect of Intramuscular FGF-2 by Repeat Dosing in a Rat Model of Peripheral Vascular Disease.

Exhibit 2

Filename : human FGF-21 cDNA in pGEM-T
Sequence Size : 643
Sequence Position: 1 - 643
Translation Position: 9 - 638;

To: T7

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10      20      30      40      50      60
agccattgatggactcggacgagaccgggttcgagcactcaggactgtgggtttctgtgc  SEQ ID NO:3
      M D S D E T G F E H S G L W V S V L  SEQ ID NO:4

70      80      90      100     110     120
tggttggtcttctgctgggagcctgccaggcacaccccatcctgactccagtcctctcc
      A G L L L G A C Q A H P I P D S S P L L

130     140     150     160     170     180
tgcaattcggggccaagtccggcagcggtacctctacacagatgatgccagcagacag
      Q F G G Q V R Q R Y L Y T D D A Q Q T E

190     200     210     220     230     240
aagcccacctggagatcagggaggatgggacgggtggggggcgctgctgaccagagccccg
      A H L E I R E D G T V G G A A D Q S P E

250     260     270     280     290     300
aaagtctcctgcagctgaaagccttgaagccgggagttattcaaattctgggagtcgaaga
      S L L Q L K A L K P G V I Q I L G V K T

310     320     330     340     350     360
catccaggttcctgtgccagcggccagatggggccctgtatggatcgctccactttgacc
      S R F L C Q R P D G A L Y G S L H F D P

370     380     390     400     410     420
ctgaggcctgcagcttccgggagctgcttcttgaggacggatacaatgtttaccagtcctg
      E A C S F R E L L L E D G Y N V Y Q S E

430     440     450     460     470     480
aagcccaaggcctcccgtgcacctgccagggaacaagtccccacaccgggaccctgcac
      A H G L P L H L P G N K S P H R D P A P

490     500     510     520     530     540
cccgaggaccagctcgcttccctgccactaccaggcctgcccccgcaactcccggagccac
      R G P A R F L P L P G L P P A L P E P P

550     560     570     580     590     600
ccggaatcctggccccccagccccccgatgtgggtcctcggaccctctgagcatggtgg
      G I L A P Q P P D V G S S D P L S M V G

610     620     630     640     650
gaccttcccaggggccgaagccccagctacgcttccctgaagcca
      P S Q G R S P S Y A S *

```

Exhibit 3

From: Mike_Kavanaugh@cc.chiron.com
Sent:
To:
Subject:

1) Exemplary peptides for antibodies include:

RQRYLYTDDAQQTEAH (residues 46-61)

HLPGNKSPHRDPAPR (residues 146-160)

(Seq ID 7)
(Seq ID 8)